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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,237	03/06/2002	Steven T. Boyce	CUT/01	8680

26875 7590 06/13/2007

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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
06/13/2007	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/092,237
Filing Date: March 06, 2002
Appellant(s): BOYCE, STEVEN T.

Beverly A. Lyman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 02/02/07appealing from the Office action mailed 04/18/06.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

- 5976878 Boyce 11-1999
- Niels et al, J Invest Dermol 97(5):843-848, 1991.
- Boyce, Med. Biol. Eng. Comput. 36:791-800, 1998.
- Supp et al. The FASEB Journal. 16:797-804, 2002.
- Naughton, Ann. N.Y. Acad Sci. 961:372-385, 2002.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

Claims 1-4, 6-7, 9-11, 13, 15, 18, 21-27, 29 and 32-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Niels et al (J Invest Dermol 97(5):843-848, 1991), for the same reasons of record as set forth in the office action mailed on 10/26/05.

The instant claims are drawn to a cultured skin device or method of producing the same comprising a cultured dermal cell on a biocompatible reticulated acellular matrix on which cultured epidermal cells are inoculated.

Niels et al teaches a cultured skin device comprising cultured dermal cells (fibroblasts) on a biocompatible acellular reticular dermal matrix, wherein the dermal cells provides a lamination layer for cultured epidermal cells (keratinocytes) deposited on the dermal cells (page 844, col.1 para. 2, page 845, col.2 para. 2). The cited art further teaches that the acellular reticular dermal matrix comprises collagen (page 845, fig-1a). The cited art further teaches preparation of cultured skin device using air-liquid interface culture system (page 844, col.1. para.1). The cited art further teaches grafting of the cultured skin device on an athymic mouse, which resulted in reconstruction of skin populated with blood vessels at day 25, wherein the overlying epidermis was viable and differentiated (page 844, col.1 para.3, page 845col.2 para. 2). Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

Claims 12, 16-17, 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niels et al (J Invest Dermol 97(5):843-848, 1991) as applied to claims 1-4, 6-7, 9-11, 13, 15, 18, 21-27, 29 and 31-37 above, and further in view of Boyce (Med. Biol. Eng. Comput. 36:791-800, 1998, ref of record) and Boyce (US 5,976,878, 1999, ref of record), for the same reasons of record as set forth in the office action mailed on 10/26/05.

The teaching of Niels et al is described above. Even though Niels teaches a method of making skin construct comprising variety of cultured cells the reference does not specifically teach a method of producing a cultured skin device in medium containing insulin in the range of 0.05 ug/ml to 500 ug/ml and incorporation of genetically engineered cells.

Boyce (1998) teaches skin substitutes comprising cultured human keratinocytes, fibroblasts, melanocytes and collagen-GAG polymers. The cited art teaches a cultured skin substitute comprising cultured dermal cells on Collagen-GAG matrix, which further provides a lamination layer for cultured keratinocytes. The cited art further teaches that components of skin substitute include keratinocytes, fibroblasts, endothelial cells, smooth muscle cell, melanocytes, nerve cells, glands and hair follicles (page 792, col. 1, table-1, page 793 fig-1). The cited art further teaches the use of skin substitutes for burns, scars cutaneous ulcers or congenital anomalies (page 791, col.1 para.1). The cited art further teaches that cells in the skin substitute ranges from culture parenchymal cells (autologous or allogenic) to tissue derivatives (i.e. xenogeneic collagens acellular dermal matrix) to synthetic polymers (page 792 col.2 para.1). With regard to claim 8 the cited art further teaches genetic modification of skin cells (page 797 col.2 para.2-3, page 794 fig-3). The cited art further teaches that the skin substitute is capable of providing epidermal barrier, basement membrane, angiogenesis and pigmentation (page 794 col.1 para.1, col.2 para.1; page 795, col.2 para.1). The cited art further teaches the use of non-adherent highly porous dressing that allow both delivery and drainage of wound exude from grafts during the period of engraftment (page 795, col.2 para.1).

Boyce (1999) teaches a composite skin construct and a method of making the skin construct. With regard to claims 11-12 and 28 Boyce (US 5,976,878, 1999) teaches a method of making a composite skin on a laminated surface of dermal membrane (collagen-GAG), wherein the human keratinocytes are cultured in a media containing 0.5 ug/ml of insulin (col.14 line 64). With regard to claim 30 the cited art teaches dehydration of collagen matrix to form a cross-linked matrix before inoculation with dermal culture (col.12 line 45-61).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to incorporate insulin in the range of 0.05 ug/ml to about 500 ug/ml in the culture conditions as taught by Niels in view of Boyce (1998). One would have been motivated to incorporate insulin in culture media because insulin is a growth factor that increases cellular growth and proliferation. It would have been further obvious to use dehydrated laminated collagen as taught by in view of Boyce (1999). One would have been motivated to make dried cross-lined matrix because such a preparation can be stored in a dry state for future use. In addition it would have been further obvious to incorporate genetically engineered cells in the skin construct in view of Boyce (1998). One would have been motivated to do so produced the desired gene product in the cultured skin construct. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claim Rejections - 35 USC § 112 *(Enablement)*

Claims 1-4, 6-7, 9-13, 15-18, 21-30, 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cultured skin device and method of making the same wherein the biocompatible reticular acellular matrix is a porous cross-linked collagen matrix, does not reasonably provide enablement for any cultured skin device, wherein the biocompatible reticular acellular matrix is composed of any other substance. In addition while being enabling for the therapeutic use of the cultured skin device for skin engraftment the specification as filed does not reasonably provide enablement for the therapy of any and all metabolic diseases, protein defect, protein deficiency and combination thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 10/26/05.

Nature of Invention:

The instant invention relates to an artificial skin construct.

Breadth of Claims and Guidance Provided in the Specification

The scope of invention as claimed encompasses an artificial skin device made of any biocompatible reticulated a cellular matrix (i.e. steel, glass, gold, plastic etc). In addition the scope of invention as claimed the use of device for the therapy of any and all metabolic diseases, protein defect, protein deficiency and combination thereof. The specification as filed fails to disclose any skin device (as claimed) that is capable of engraftment in an animal and can be of any therapeutic use in a patient with a burn, a burn scar, a chronic skin ulcer, a congenital skin lesion, any metabolic disease, any protein defect, any protein deficiency, and/or combinations thereof. The examples provided in the specification as filed are prophetic and read as instructions rather than examples, leaving significant amount of experimentation necessary to practice the invention.

State of Art and Unpredictability

The state of the artificial skin art at the time of filing of instant invention was such that the construction artificial skin is complex and the final product made is of little benefit if it cannot be efficiently produced, and is capable of providing engraftment benefits (see Supp et al. *The FASEB Journal.* 16:797-804, 2002, see page 803, col.1, ref. of record). The specification as filed fails to disclose any skin device (as claimed) which is capable of engraftment in an animal and can be of any therapeutic use in a patient with a burn, a burn scar, a chronic skin ulcer, a congenital skin lesion, any metabolic disease, any protein defect, any protein deficiency, and/or combinations thereof. For example, even if one skilled in the art is able to construct the claimed cultured skin device using a *polycarbonate-based non-porous reticulated acellular matrix*, it is unclear how one skill in the art would use such a device for the therapy of a burn, a burn scar, a chronic skin ulcer, a congenital skin lesion, a metabolic disease, a protein defect, a protein deficiency and combination thereof. The applicant's specification fails to provide an enabling disclosure in this context. Furthermore the state of the art regarding the selection of the matrix onto which the cells are seeded suggest that the choice of the matrix has been found to be key to the uniform formation of tissue, since the matrix provides physical and chemical cues to guide the process of

artificial skin development. In addition the spatial and compositional properties of the matrix are key, with porosity of the scaffold and inter connectivity of the pores being capable of enabling cell penetration into the structure as well as transport of nutrients and waste products (Naughton, Ann. N.Y. Acad Sci. 961:372-385, 2002). The applicant fails to provide any evidence on the record, which establishes that a skin device constructed on a non-porous acellular matrix is capable of engrafting for the therapy of a burn, a burn scar, a chronic skin ulcer, a congenital skin lesion, a metabolic disease, a protein defect, a protein deficiency and combination thereof. For example, the applicant fails to provide an enabling disclosure for therapy in a patient having a metabolic disease like type-1 diabetes, wherein the protein deficiency is insulin production. For any such therapy there exist a need for a greater understanding of an underlying mechanism that contribute to a disorder. The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). In instant case the examples provided in the instant specification are prophetic and read as instructions rather than examples, leaving significant amount of experimentation necessary to practice the invention. The USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

Furthermore while every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case the specification as filed read upon instructions rather than providing a working example, leaving significant amount of experimentation necessary to practice the invention. For example the specification fails to disclose making of a

cultured skin device comparing any and all biocompatible reticulated acellular non-porous matrices (i.e. steel, glass, gold, plastic etc), and successful engraftment of any such device in any animal model to establish that such a skin device is capable of performing the intended use of at least for skin engraftment. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966).* Therefore the rejection of instant claims falls in the realm of 35 USC 112(1) regarding enablement issues (how to make and use the claimed skin device) and not under 35 USC 112(1) for utility issues. In addition making an artificial skin device using any combination of conditions and components wherein the fate of the final product is unpredictable, is not considered routine in the art and without sufficient disclosure of the final product made the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim Rejections - 35 USC § 112 (indefiniteness)

Claims 10-17, 18-23, 24-27 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the same reasons of record as set forth in the office action mailed on 10/26/05.

Claim 10 is indefinite because it is unclear what are conditions sufficient to form a cultured skin device so that the dermal cells provide a cellular lamination layer in this context. It is unclear whether the dermal and epidermal cells are inoculated as a mixture or separately in this context. The applicant argues that instant claims are distinct because either sequential or simultaneous inoculation is possible. However this is found

not persuasive because the scope of conditions sufficient to form a cultured skin device is not limited to equential or simultaneous inoculation of cells.

Claim 18 is indefinite because it is unclear what are the conditions to form at least one dermal cellular lamination layer in this context. The applicant argues that claim 18 has been amended to recite "dermal cell". The applicant response has been found not fully persuasive because scope of conditions sufficient to form a cultured skin device is not limited to the identification of first dermal cell.

Claim 24 is indefinite because it is unclear what are conditions to form a permanent cultured skin device having a dermal cellular lamination layer. It is especially unclear in context that whether the dermal and epidermal cells are inoculated as a mixture or separately for the production of the permanent cultured skin device. The applicant argues that instant claims are distinct because either sequential or simultaneous inoculation is possible. However this is found not persuasive because the scope of conditions sufficient to form a cultured skin device is not limited to sequential or simultaneous inoculation of cells.

Claim 34 is indefinite because it is unclear what are conditions to form a permanent cultured skin device within one month having a cellular lamination layer. It is unclear whether the dermal and epidermal cells are inoculated as a mixture or separately in this context. The applicant argues that instant claims are distinct because either sequential or simultaneous inoculation is possible. However this is found not persuasive because the scope of conditions sufficient to form a cultured skin device is not limited to sequential or simultaneous inoculation of cells.

In addition if the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand **how to avoid infringement**, a rejection of the claim under 35 U.S.C. 112, second paragraph would be appropriate. See Morton Int 'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993). See MPEP 173.02. In instant case it is unclear how one would envision the invention as claimed to avoid infringement issues especially in context with "conditions sufficient to form" in the context of instant claims.

(10) Response to Argument

The instant invention is drawn to an artificial skin device which is capable of engraftment in an animal which is intended for a therapeutic use in a patient with a burn, a burn scar, a chronic skin ulcer, a congenital skin lesion, any metabolic disease, any protein defect, any protein deficiency, and/or combinations thereof

The state of the artificial skin art at the time of filing of instant invention was such that the construction of multilayered artificial skin is considered complex and the final product made is of little benefit if it cannot be efficiently produced, and is capable of providing engraftment benefits. In addition, the choice of the matrix has been found to be key in the uniform formation of tissue, since the matrix provides physical and chemical cues to guide the process of artificial skin development under highly orchestrated culture conditions.

The evidence Appendix A is the 1st declaration by Steven T. Boyce filed 03/26/04 provided to over come the prior art rejection (dated 10/21/03) over inventors own publication Boyce Med Bio. Eng & Comp. 36:791-800, 1998.

The evidence Appendix B is a Power Point slides presented during interview conducted on 07/20/05. However, the composition of biocompatible reticulated matrix was not disclosed.

The 2nd declaration by Steven T Boyce filed 08/02/05 states that "In contrast, all of my claims recite a matrix that is reticulated. Such a matrix is continuous and has no perforations. My specification clearly distinguishes a perforated matrix from a reticulated matrix, and itself provide support why it is not obvious to substitute a perforated matrix for my matrix" see declaration filed 08/02/05 pages 2-3.

Claim Rejections - 35 USC § 102 *(Response to Arguments)*

Claims 1-4, 6-7, 9-11, 13, 15, 18, 21-27, 29 and 32-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Niels et al (J Invest Dermol 97(5):843-848, 1991), for the same reasons of record as set forth in the office action mailed on 10/26/05.

Regarding the device claims 1-4, 6-7 and 9 the applicant argues that the appellant's engineered matrix is fabricated from chemical reagents. The applicant argues that Niels does not disclose an engineered matrix, as the term is properly construed, and thus does not anticipate claims 1-4, 6-7, and 9. The applicnat argues that in contrast to Appellant's chemically fabricated matrix, Niels obtains human cadaver skin, which is an ex-vivo biologic. As only one striking illustration of the distinction, Niels would have to obtain permission to prepare his substrate, because it uses skin harvested from the back or thigh of a cadaver. The applicant states that the matrix of cited art is the irradiated harvested skin (to devitalize it), soaked in antibiotics (to sterilize it), and have a portion removed of it to obtain de-epidermized dermis (see Niels p. 843, col. 2). The applicant argues that in appellant's device, the cellular lamination layer is provided by dermal cells that are asymmetrically distributed on the outer surface of the matrix whereas in Niels' device, the dermal cells are required to invade the substrate. The applicant argues that fibroblasts, which are dermal cells, that invade Niels' acellular dermis substrate do not meet appellant's claimed limitation

However, applicant's arguments are found not persuasive because the scope of invention as claimed is NOT limited to a "chemically engineered matrix" as asserted herein by the applicant. Given the broadest reasonable interpretation the scope of invention as claim encompasses any biocompatible reticulated acellular matrix that has been engineered by man, which clearly reads upon the biocompatible acellular reticular dermal matrix as disclosed by Niels et al (see Niels page 843, col.2, especially the making of DED and SCD). As acknowledged even by that applicant cited art clearly teaches irradiattion of the harvested skin (to devitalize it), soaking it in antibiotics (to sterilize it), and removing a portion of it to obtain de-epidermized dermis (see Niels p. 843, col. 2), which clearly encompasses the engineering of a biocompatible marix. Since the biocompatible marix as claimed is not limited to an engineered matrix prepared or fabricated from chemicals, the cited art clearly anticipate the invention as claimed.

Furthermore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which

applicant relies (*i.e., a) Chemically manufactured biocompatible matrix, b) wherein the biocompatible matrix is non-invasive to dermal cells*) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition the MPEP clearly states that the claims define the property rights provided by a patent, and thus require careful scrutiny. The goal of claim analysis is to identify the boundaries of the protection sought by the applicant and to understand how the claims relate to and define what the applicant has indicated is the invention. See *In re Hiniker Co., 150 F.3d 1362, 1369, 47 USPQ2d 1523, 1529 (Fed. Cir. 1998).* The subject matter of a properly construed claim is defined by the terms that limit its scope. As a general matter, the grammar and intended meaning of terms used in a claim will dictate whether the language limits the claim scope. Language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation. In instant case the given the broadest reasonable interpretation the "an engineered" product is merely a product that has been altered in context to its original form. Thus, the cited art clearly anticipate the invention as claimed.

Regarding the method of producing the device (claims 10-13, 15-18, 21-27, and 29-30), the applicant argues that the proper claim construction of an engineered matrix is "*one that is synthesized from chemicals and fabricated to desired specifications*", and the proper claim construction of a dermal cell lamination layer is one with dermal cells on the surface of the matrix but not required to invade the matrix. The applicant argues that cited art does not disclose an engineered matrix, nor does the cited art have a cellular lamination layer, as the terms are properly construed.

However the applicant's arguments are found not persuasive for the reason of record as set forth above, which clearly concludes that the scope of biocompatible matrix as claimed is NOT limited to "*one that is synthesized from chemicals and fabricated to desired specifications*" but encompasses the biocompatible matrix disclosed by Niels which is made by engineering the cadaver skin the desired specification (i.e. irradiation, antibiotics treament and removal of a portion of it to obtain

de-epidermized dermis). Thus given the broadest reasonable interpretation the cited art clearly anticipate the method of producing cultured skin device that requires the use of the biocompatible matrix disclose by Niels.

Regarding the method of inoculating a Matrix (claims 32-33), the applicant argues that the proper claim construction of an engineered matrix having a cellular lamination layer of dermal cells is a matrix that is synthesized from chemicals and fabricated to desired specifications, and one that has dermal cells on the surface of the matrix that are not required to invade the matrix. The applicant argues that Niels does not disclose such a matrix, as the terms are properly construed, and thus does not anticipate claim 32 nor dependent claim 33.

However the applicant's arguments are found not persuasive for the reasons as set forth above because given the broadest reasonable interpretation Niels clearly teaches the biocompatible matrix as claimed. In addition the cited art teaches the sequential seeding of fibroblast and keratinocytes on the matrix and in the presence of culture media (see page 844, col.1, para. 2-3; col.2 para.4-5). Thus given the broadest reasonable interpretation to the invention as claimed the cited art clearly anticipate the invention as claimed.

Regarding a method of producing a permanent skin device (claims 34-37), the applicant argues that Niels specifically discloses "Seeding cultured dermal fibroblasts on SCD [second cut dermis] resulted in both colonization of the surface as well as invasion of the acellular dermis" (Niels p. 845 middle of col. 2, emphasis added). The applicant argues that fibroblasts, which are dermal cells that invade Niels acellular dermis do not meet appellant's claimed limitation that requires a cellular lamination layer in which cells do not invade the matrix.

However the applicant's arguments are found not persuasive for the reasons as set forth above because given the broadest reasonable interpretation Niels clearly teaches the biocompatible matrix as claimed. In addition applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (*i.e., wherein the biocompatible matrix is non-invasive to dermal cells*) are not recited in the rejected claim(s). Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus given the broadest reasonable interpretation to the invention as claimed the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103 *(Response to Arguments)*

Claims 12, 16-17, 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niels et al (J Invest Dermol 97(5):843-848, 1991) as applied to claims 1-7, 9-11, 13-15, 18-27, 29 and 31-37 above, and further in view of Boyce (Med. Biol. Eng. Comput. 36:791-800, 1998, ref of record) and Boyce (US 5,976,878, 1999, ref of record), for the same reasons of record as set forth in the office action mailed on 10/26/05.

Regarding the method of producing the device (Claims 12, 16-17, and 30), the applicant argues that to render Appellant's claims obvious, combination of cited references must teach or suggest all of the claim limitations, and there must be a reasonable expectation of success that the claimed invention will result if the references are so combined, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Niels and the secondary references or to combine their teachings. The applicant continues that one cannot pick and choose from references only what is needed to support a given position, and exclude other parts necessary to appreciate what the references as a whole suggests. The applicant argues that Niels and the secondary references must be viewed without the benefit of impermissible hindsight. The applicant argues that Niels and the secondary references must also provide the basis for the modification; they cannot merely make it obvious to try the claimed invention. The applicant argues that Even if the prior art may be modified, the prior art must have suggested the desirability of the modification.

The applicant argues that claim 12, requires specific insulin concentrations in the medium in which the inoculated matrix is incubated. The applicant argues that Niels,

directed to use of allogenic (cadaver) acellular dermis, does not use a medium for incubating an engineered matrix and does not add insulin in the medium. The applicant argues that Boyce 1998 discloses a completely different device, one in which the matrix is filled uniformly and entirely with cultured dermal cells. The applicant argues that the invention as claimed recites a matrix where the dermal cells provide a cellular lamination layer. The applicant argues that because Niels in view of Boyce 1998 does not meet all the claim limitations the invention as claimed is not obvious over cited prior art of record.

However the applicant's arguments are found not persuasive because the applicant only considered Niels in view of Boyce 1998 and fails to consider the instant rejection in view of Boyce 1999 (USPN 5,976,878) who clearly teaches a method of making a composite skin on a laminated surface of dermal membrane (collagen-GAG), wherein the human keratinocytes are cultured in a media containing 0.5 ug/ml of insulin (col.14 line 64). With regard to claim 30 the cited art teaches dehydration of collagen matrix to form a cross-linked matrix before inoculation with dermal culture (col.12 line 45-61). Thus the cited art clearly teaches the instant claim limitations.

The applicant argues that Claims 16-17 also depend from claim 10, and recite specific cells inoculated on the matrix used in the method. Again, this matrix is the engineered matrix of claim 10, and Appellant's above analysis with respect to claim 12 applies with respect to claims 16-17. The applicant argues that the examiner points to no teachings in the references in support for his statement that the specific cells recited in claims 16-17 are obvious.

However the applicant's arguments are found not persuasive. The applicant fails to consider Boyce 1998, who clearly teaches that components of skin substitute include keratinocytes, fibroblasts, endothelial cells, smooth muscle cell, melanocytes, nerve cells, glands and hair follicles (see Boyce 1998, page 792, col. 1, table-1, page 793 fig-1). Thus the cited art clearly teaches the instant claim limitations.

The applicant argues that claim 30 depends from claim 29 and requires that the matrix be crosslinked before inoculation with dermal cells. Again, this matrix is the engineered matrix of claim 29, and Appellant's above analysis of differences in the

matrix applies to claim 30. The applicant argues that Niels has no disclosure whatsoever to a crosslinked matrix, and his use of cadaver skin teaches away from crosslinking (i.e., there are no crosslinkable components) so that the secondary references fail and the rejection cannot stand.

However the applicant's arguments are found not persuasive. The applicant fails to consider teaching in Boyce 1999 (USPN 5,976,878) who clearly teaches teaches dehydration of collagen matrix to form a cross-linked matrix before inoculation with dermal culture (col.12 line 45-61).

The applicant argues that one skilled in the art would not be taught, motivated, or suggested to omit or add a component, or to change a concentration of any component, at least because there is no suggestion to do so in these references and there is no reasonable expectation of success that doing so would result in the desired outcome. The applicant argues that "*in contrast, requiring specific components at specified concentrations teaches away from any change, because of the possibility that such change would perturb the balance required for growth and maintenance of specific cell types*".

However the applicant's arguments are found not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated above the scope of invention as claim encompasses any biocompatible reticulated acellular matrix that has been engineered by man, which clearly reads upon the biocompatible acellular reticular dermal matrix as disclosed by Niels (see page 843, col.2, especially the making of DED and SCD). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention

where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one ordinary skill in the art at the time of filing to incorporate insulin in the range of 0.05 ug/ml to about 500 ug/ml in the culture conditions as taught by Niels in view of Boyce (1999). One would have been motivated to incorporate insulin in culture media because insulin is a growth factor that increases cellular growth and proliferation. It would have been further obvious to use dehydrated laminated collagen as taught by in view of Boyce (1999). One would have been motivated to make dried cross-lined matrix because such a preparation can be stored in a dry state for future use. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claim Rejections - 35 USC § 112 Enablement *(Response to Arguments)*

Claims *1-4, 6-7, 9-13, 15-18, 21-30, 32-37* are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cultured skin device and method of making the same wherein the biocompatible reticular acellular matrix is a porous cross-linked collagen matrix, does not reasonably provide enablement for any cultured skin device, wherein the biocompatible reticular acellular matrix is composed of any other substance. In addition while being enabling for the therapeutic use of the cultured skin device for skin engraftment the specification as filed does not reasonably provide enablement for the therapy of any and all metabolic diseases, protein defect, protein deficiency and combination thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 10/26/05.

Regarding claims 1-4, 6-7, and 9 the applicant argues that the matrix is enabled, at least at pp. 12-15, sections "Matrix-Forming Protein-Containing Fluid" and "Method of Forming Crosslinked Matrix", and in Appellant's U.S. Patent No. 6,905,105,

incorporated by reference at p. 13 in the present application. The applicant argues that the cell sources are enabled at least at pp. 9-11 disclosing sources of dermal and epidermal cells. The applicant argues that the conditions to form the device are enabled at least using standard tissue culture techniques known to one skilled in the art.

However the applicants arguments are found not persuasive because given the broadest reasonable interpretation the scope of the biocompatible reticulated a cellular matrix, encompasses a non-porous acelluar matrix (i.e. steel, glass, gold, plastic etc) comprising collagen. The state of the artificial skin art at the time of filing of instant invention was such that the construction artificial skin is complex and the final product made is of little benefit if it cannot be efficiently produced, and is capable of providing engraftment benefits (see Supp et al. *The FASEB Journal.* 16:797-804, 2002, see page 803, col.1, ref. of record). Furthermore the earlier office action provides clear evidence that state of the art regarding the selection of the matrix onto which the cells are seeded suggest that the choice of the matrix has been found to be key to the uniform formation of tissue, since the matrix provides physical and chemical cues to guide the process of artificial skin development. In addition the spatial and compositional properties of the matrix are key, with porosity of the scaffold and inter connectivity of the pores being capable of enabling cell penetration into the structure as well as transport of nutrients and waste products (see Naughton, Ann. N.Y. Acad Sci. 961:372-385, 2002). Furthermore, even though the presentation provided by the applicant during the interview conducted on 07/22/05 discloses use of a biocompatible reticulated matrix, the presentation (Appendix B, Slide 2) falls short of disclosing the structural limitation of the biocompatible acellular matrix used.

Regarding method (claims 10-13, 15-18, 21-27, and 29-30) the applicant takes the same position that since the matrix as claimed enabled, the condition to form the device are also enabled using standard tissue culture techniques known to one skilled in the art. Regarding claim 28 the applicant takes the similar position that since the matrix as claimed enabled, the condition to form the device are enabled using standard tissue culture techniques known to one skilled in the art. In addition the applicant argues

that specific medium components and concentrations, with vendors and other details are provided in the specification.

However the applicant's arguments are found not persuasive for the reason of record as set forth above regarding the scope of biocompatible acellular matrix. In addition the limitation recited in the claim 28 are mere culture media contents to culture the dermal cell on the engineered biocompatible matrix, wherein the structural limitations of the matrix use has not been recited in the invention as claimed. Thus it would require and undue amount of experimentation to use any engineered biocompatible matrix to make the skin device as claimed.

Regarding a Method of inoculating a Matrix (claims 32-33), the applicant takes same position that since the matrix as claimed enabled, the condition to form the device are also enabled using standard tissue culture techniques known to one skilled in the art. The applicant further argues that the claimed method of inoculating the matrix by which culture medium is provided to a top surface of the matrix under conditions sufficient to draw the medium through the absorbent material and deposit dermal cells on the matrix is the "lifted inoculation" an embodiment that is described in the specification. In addition the applicant argues that disclosing the matrix, its preparation, its composition, and its dimensions, examples and vendors of types of porous membranes, absorbent materials, and medium used to inoculate dermal cells, and conditions for post-inoculation treatment of the membrane to form a cellular lamination layer enables the invention as claimed.

However this is found not persuasive because the engineered reticulated a cellular matrix as claimed herein is indeed a non-porous structure that would not allow the drawing of media through the adsorbent material. The earlier office action has provide a clear evidence that use of a non-porous matrix is considered highly unpredictable *(especially in view of applicants 2nd declaration filed 08/02/05 that states the matrix of instant invention is non-porous)* because the spatial and compositional properties of the matrix are key, with porosity of the scaffold and inter connectivity of the pores being capable of enabling cell penetration into the structure as well as transport of nutrients and waste products (see Naughton, Ann. N.Y. Acad Sci. 961:372-385, 2002).

Regarding a method for producing a Permanent Skin Device for a Patient (claims 324-37), the applicant argues that in view of guidance provided in the specification one skill in the art would be able to make and use the invention as claimed depending upon the reason for which the device was transplanted; (e.g., therapy for a burn for devices transplanted to a newly burned patient, therapy for a burn scar for devices transplanted to scared burned patients, therapy for a chronic skin ulcer for devices transplanted to patients with a chronic skin ulcer, therapy for metabolic disease transplanted to a patient with such a disease from which a cultured skin device may provide a missing or defective component, therapy for a protein defect transplanted to a patient with such a defect from which a cultured skin device may provide the missing protein, protein precursor, cofactor, etc., therapy for a protein deficiency for devices transplanted to a patient with such a deficiency from which a cultured skin device may provide or supplement the deficient protein, protein precursor, cofactor, etc). The applicant argues that the specification provides additional efficacy (*by merely stating not providing any working example*) for the making and using the claimed skin device for transplantation. The applicant further argues that evidence provided in the Appendix B photographs show the making and use of such artificial skin device. The applicant argues that the matrix (slide 2), that is "acellular" and that is "engineered" as disclosed in the specification and using the device in Appellant's now issued U.S. Patent No. 6,905,105". The applicant argues that the presentation shows "dermal cells providing a cellular lamination layer for epidermal cells" and the engraftment of the device on a burn victim.

However the applicant's arguments are found not persuasive because neither at the time of interview nor in any subsequent response afterward the applicant fails to provide any declaration that the matrix used to construct the skin device disclose in the Appendix B (slide 2) indeed is "acellular" and that is "engineered" as disclosed in the specification and using the device in Appellant's now issued U.S. Patent No. 6,905,105".

To address the lack of any working example wherein an actual skin device as claimed has been constructed using the guidance provided in the specification as field the applicant argues that the applicant wrote description without an example section thus obviating the need of tense specific language. The applicant argues that all processes were indeed performed and the applicant presented color photographs of

slide 5 (Appendix B), which provides evidence that invention as claimed is enabled showing a patient treated with the method as claimed.

However the applicant's arguments are found not persuasive for the reason of record as set forth above regarding the making of engineered biocompatible matrix which applicant admits is a non-porous. The applicant fails to provide any evidence on record regarding the composition of the matrix used in the making of skin device disclosed in Appendix B and especially in view of applicants 2nd declaration filed 08/02/05 which clearly states that "*Such a matrix is continuous and has no perforations*". The earlier office action has provide a clear evidence that use of a non-porous matrix is considered highly unpredictable because the spatial and compositional properties of the matrix are key, with porosity of the scaffold and inter connectivity of the pores being capable of enabling cell penetration into the structure as well as transport of nutrients and waste products (see Naughton, Ann. N.Y. Acad Sci. 961:372-385, 2002). In addition the applicant fails to provide any evidence on the record, which establishes that a skin device constructed on a non-porous acellular matrix is capable of engrafting for the therapy of a burn, a burn scar, a chronic skin ulcer, a congenital skin lesion, a metabolic disease, a protein defect, a protein deficiency and combination thereof.

Furthermore while every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case the specification as filed read upon instructions rather than providing a working example, leaving significant amount of experimentation necessary to practice the invention. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966).* In addition making an artificial skin device using any combination of conditions and components wherein the fate of the final product is unpredictable, is not considered routine in the art and without sufficient disclosure of the final product made the experimentation left to those skilled in the art is unnecessarily, and improperly,

extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988).

Claim Rejections - 35 USC § 112 Second: indefinite *(Response to Arguments)*

Claims 10-13, 15-17, 18, 21-27 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the same reasons of record as set forth in the office action mailed on 10/26/05.

Claim 10 is indefinite because it is unclear what are conditions sufficient to form a cultured skin device so that the dermal cells provide a cellular lamination layer in this context. The applicant argues that claim is not indefinite because one skilled in the art, would know that infringement occurred if he/she met the claim limitations and inoculated either sequentially or simultaneously, at least because (a) no temporal limitation is recited in claim 10, and (b) because the content of the disclosure clearly and precisely permits either case.

However the applicant's arguments are found not persuasive because the metes and bounds of "conditions sufficient to form a cultured skin device" are not clear and the scope of the instant claim is not limited to sequential or simultaneous inoculation of cells as asserted by the applicant.

Claim 18 is indefinite because it is unclear what are the conditions to form at least one dermal cellular lamination layer in this context.

The applicant argues that one skilled in the art, however, would know the scope of the claimed "conditions to form at least one dermal cellular lamination layer population" because these are "conditions facilitating cell growth, maintenance, and division" that is standard tissue culture conditions. The applicant argues that one skilled in the art would therefore know these conditions, and further would know if infringement occurred by determining if "at least one dermal cellular lamination layer population" resulted from the conditions. The applicant concluded that because one skilled in the art

would know both the scope of the claims and would know when infringement occurred the assets claim 18 is sufficiently definite.

However, the applicant response has been found not persuasive because the metes and bounds of conditions sufficient to form a cultured skin device are not clear. Furthermore contrary to applicants arguments the standard tissue culture conditions would not lead to the formation at least one dermal cellular lamination layer because standard tissue culture condition produces a monolayer and not a cellular lamination layer which constitutes multiple layers of dermal cells *(see lamination (noun): a layered structure).*

Claim 24 is indefinite because it is unclear what are conditions to form a permanent cultured skin device having a dermal cellular lamination layer. It is especially unclear in context that whether the dermal and epidermal cells are inoculated as a mixture or separately for the production of the permanent cultured skin device.

The applicant argues that one skilled in the art, however, would know the scope of the claimed "conditions to form at least one dermal cellular lamination layer population" because these are "conditions facilitating cell growth, maintenance, and division" that is standard tissue culture conditions. The applicant argues that one skilled in the art would therefore know these conditions, and further would know if infringement occurred by determining if "at least one dermal cellular lamination layer population" resulted from the conditions. The applicant concluded that because one skilled in the art would know both the scope of the claims and would know when infringement occurred the assets instant claim is sufficiently definite.

However, the applicant response has been found not persuasive because the metes and bounds of conditions sufficient to form a cultured skin device are not clear. Furthermore contrary to applicants arguments the standard tissue culture conditions would not lead to the formation at least one dermal cellular lamination layer because standard tissue culture condition produces a monolayer and not a cellular lamination layer which constitutes multiple layers of dermal cells *(see lamination (noun): a layered structure).*

Claim 34 is indefinite because it is unclear what are conditions to form a permanent cultured skin device within one month having a cellular lamination layer. It is unclear whether the dermal and epidermal cells are inoculated as a mixture or separately in this context.

The applicant argues that one skilled in the art would know the scope of the claimed "conditions to form a cultured skin device having a cellular lamination layer on the biocompatible reticulated acellular matrix within one month after inoculating the cells", because these are "conditions facilitating cell growth, maintenance, and division", that is, standard tissue culture conditions. The applicant argues that one skilled in the art would certainly know these conditions, and further would know if infringement occurred by determining if "at least one dermal cellular lamination layer population" resulted from the conditions, particularly because the temporal limitation adds still further definiteness: the lamination layer must form "within one month after inoculating the cells"

However, the applicant response has been found not persuasive because the metes and bounds of conditions sufficient to form a cultured skin device within one month are not clear. Furthermore contrary to applicants arguments the standard tissue culture conditions would not lead to the formation at least one dermal cellular lamination layer because standard tissue culture condition produces a monolayer and not a cellular lamination layer which constitutes multiple layers of dermal cells *(see lamination (noun): a layered structure).*

In addition the MPEP clearly states that the claims define the property rights provided by a patent, and thus require careful scrutiny. The goal of claim analysis is to identify the boundaries of the protection sought by the applicant and to understand how the claims relate to and define what the applicant has indicated is the invention. Furthermore, claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims. Raytheon Co. v. Roper Corp., 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984). See also MPEP § 2111 - § 2111.01. Limitations appearing in the

specification but not recited in the claim are not read into the claim. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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